REMARKS

Claims 1, 2, 4-8, 10-14 and 19-20 are pending. Claims 21 and 22 are cancelled without prejudice. Amendments to claims 1, 2, 8, 10, 11, 13, 14, 19 and 20 are proposed herein. The amendments add no new matter.

It was noted upon review of the claims that the term "labeled" is occasionally spelled "labelled." While "labeled" is one of the few words for which there is more than one correct spelling, i.e., both are correct, for consistency, an amendment to each of the claims where the term appears (i.e., claims 1, 2, 8, 10, 11, 13, 14, 19 and 20) is proposed herein such that the claims uniformly recite "labeled." This amendment is clearly not a narrowing amendment and is not made for any reason pertaining to patentability.

Rejections under 35 U.S.C. §112, Second Paragraph:

Claims 1, 4-8 and 10-14 are rejected as indefinite under 35 U.S.C. §112, second paragraph.

Claim 1 is rejected as indefinite for use of the phrase "wherein detection of a signal generated by said labeled first binding partner and/or labeled second binding partner is an indicator of the conformational state of the protein." The Office Action states that it is unclear how the conformational state of the protein is detected or determined when the signal generated is only that of the labeled second binding partner which binds the protein independent of the conformational state of the protein.

Applicants submit that claim 1 requires that the labeled second binding partner "generates a signal *in a manner dependent on the binding of the first binding partner to the protein.*" Thus, where a signal from the second labeled binding partner is detected, there must be binding of the first labeled binding partner to the target protein. Thus, for a signal to be detected from the second labeled binding partner, the target protein must be present in a conformation that can be bound by the labeled first binding partner, and the assay works even if the signal detected is only that from the labeled second binding partner which binds to the protein independent of the conformational state of the protein. In view of this, Applicants submit that claim 1 is clear as

currently pending. Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

Statutory Double Patenting:

Claims 1, 4-8, 10-14 and 19-22 are provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 1-13 and 18-21 of co-pending Application No. 09/258,452. Applicants submit that Application No. 09/258,452 has been abandoned. As such, the current provisional rejection over the claims of that application should be withdrawn.

Rejection under 35 U.S.C. §103(a):

In rejecting claims 19-22 as obvious under §103(a) in view of Prusiner et al., and Foster et al., the Office Action states that:

> "Applicant argues that the combination of Prusiner et al. with Foster et al. do not suggest the kit of the claimed invention. Applicant specifically argues that Prusiner et al. do not teach a first labeled binding partner which binds to the protein in a manner dependent on the conformational state of the protein and a second labeled binding partner that is independent of the conformational state of the protein and generates a signal in a manner dependent on the binding of the binding partner to the protein. According to Applicant, Foster et al. do not remedy the deficiency of Prusiner et al.; therefore, the combination of Prusiner et al. with Foster et al. does not render the claimed invention obvious.
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> "In response, Prusiner et al., indeed, additionally teach a second binding partner, i.e., antibody, which binds to the protein depending upon the conformational state of the protein, in a sandwich format of an assay (see column 16, lines 25-38)."

Applicants respectfully disagree.

Applicants submit that the Prusiner et al. reference does not teach a *labeled* first binding partner and a *labeled* second binding partner. The passage cited in the Office Action as support for the presence of a second binding partner in the method taught by Prusiner et al. is as follows:

> The assay can detect prpsc in mixtures (by direct method) where the concentration of PrP^{Sc} is less than 1% of the concentration of PrPC. *Additional sensitivity can be achieved by immunoprecipitation, using a sandwich format for a solid state assay*, differential centrifugation with detergent extraction to remove

> PrP^C, the indirect transgenic animal method or combinations of these methods. (Prusiner et al., col. 16, lines 25-31)

Applicants submit that reference to "using a sandwich format for a solid state assay" does not teach or suggest the use of first and second *labeled* binding partners as required by independent claims 19 and 20. That is, while a sandwich assay may have two binding partners, there is no requirement that both binding partners be *labeled*. For example, the Immunology textbook "Cellular and Molecular Immunology," by Abbas, Lichtman & Pober, 1991, W.B. Saunders Co., Philadelphia, describes a sandwich assay as follows:

> **Sandwich ELISA or RIA**
>
> A fixed quantity of one antibody is attached to a solid support. A test solution of unknown antigen concentration or a series of standard solutions of known concentrations of antigen is allowed to bind. Unbound antigen is removed, and a second population of enzyme-linked or radiolabeled indicator antibodies is allowed to bind. The more antigen in the test or standard solutions, the more enzyme-linked or radiolabeled second antibody will bind. The results from the standard solutions are used to construct a binding curve for second antibody binding as a function of antigen concentration, from which the quantity of antigen in the test solution may be inferred. When this test is performed with two antibodies, it is essential that these antibodies see non-overlapping determinants on the antigen; otherwise, the second antibody cannot bind. (Abbas, Lichtman & Pober, p. 61-62)

The Abbas et al. textbook also refers to Figure 3-17 (not reproduced here), the legend to which states:

> "**Sandwich ELISA or RIA.** With a fixed amount of one immobilized antibody, the binding of a second, labeled antibody increases as the concentration of antigen increases, allowing quantification of antigen."

Applicants note that this description of a standard sandwich immunoassay involves only *one* labeled antibody. There is also no teaching that signal from the labeled antibody is generated "in a manner dependent on the binding of the first binding partner to the protein," as required by claim 19, or is "detectable in a manner dependent on the binding of the first binding partner to the protein," as required by claim 20. To the contrary, an enzyme label or radiolabel will generate signal independent of the binding of the first binding partner to the protein.

In addition to the Abbas et al. text, sandwich assays are also described in the immunology textbook "ImmunoBiology: The Immune System in Health and Disease," by Janeway, Travers, Walport & Capra, 1999, Elsevier Science Ltd./Garland Publishing, New York, as follows:

> A more specific assay is a modification of ELISA known as a **capture** or **sandwich ELISA**. In this assay, the cytokine is characterized by its ability to bridge between two monoclonal antibodies reacting with different epitopes on the cytokine molecule (Fig. 2.29)." (p. 61; bolds in original)

The legend to Fig. 2.29 (not reproduced here) states:

> **Fig. 2.29 Measurement of interleukin-2 (IL-2) production by sandwich ELISA.** When T cells are activated with a mitogen or antigen they usually release the T-cell growth factor IL-2. In this assay, one unlabeled anti-IL-2 antibody is attached to the plastic, and then the IL-2 containing fluid is added. After washing, bound IL-2 is detected by binding a second, labeled anti-IL-2 antibody directed at a different epitope. This assay is highly specific because cytokines and other antigens that cross-react with one antibody are very unlikely to cross-react with the other. (p. 61, bold in original)

Here again, Applicants submit that the textbook description of a sandwich assay does not teach the use of two labeled binding partners. In the Janeway text, the first antibody is specifically stated to be an "unlabeled anti-IL-2 antibody" and the second antibody is stated to be "a second, labeled anti-IL-2 antibody." Here also, there is no teaching that signal from the labeled antibody is generated in a manner dependent on the binding of the first binding partner to the protein.

In view of the above, Applicants submit that one skilled in the art would not infer from the cited statement in the Prusiner et al. reference "Additional sensitivity can be achieved by immunoprecipitation, using a sandwich format for a solid state assay," that the reference teaches or suggests the use or presence of "a labeled first binding partner" and "a labeled second binding partner," i.e., two labeled binding partners, as required by claims 19 and 20. Applicants further submit that one of skill in the art would not find a teaching or suggestion that the second labeled binding partner generates a signal "in a manner dependent on the binding of the first binding partner to the protein," as required by claim 19, or "which is detectable in a manner dependent on the binding of the first binding partner to the protein" as required by claim 20.

In view of the above, Applicants submit that the Prusiner et al. reference does not teach or suggest all elements of claims 19 and 20 (the cancellation of claims 21 and 22 renders the

rejection moot with respect to these claims. Further, Applicants submit that the Foster et al. reference fails to remedy the deficiencies of the Prusiner et al. reference with regard to the claimed invention. As such, it is submitted that the present combination of references does not render obvious the invention of claims 19 and 20. Applicants therefore respectfully request the withdrawal of this §103 rejection of these claims.

In view of the above, Applicants submit that all issues raised in the Final Office Action have been addressed. Reconsideration of the claims is respectfully requested.

Respectfully submitted,

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